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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Meier, W. et al.

Filing Date: July 13, 2000 **Examiner: G. Kishore**

Serial No.: 09/615,305 **Art Unit: 1615**

Title: Amphiphilic Copolymer Vesicles

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APPEAL BRIEF

The following comments are submitted in Appeal of the above referenced patent application. This Appeal Brief is submitted in triplicate and accompanied by the fee set forth in 37 CFR §1.17(c) ($330.00).

(1) Real party in interest

The real party in interest in this Appeal is the Assignee, BioCure, Inc.

(2) Related appeals and interferences

There are no related appeals or interferences.

(3) Status of claims

Claims 1, 3-6, 9-14, 16-20, 27-30 are pending and on appeal. Claims 2, 7, 8, 15, 21-26 have been cancelled.

(4) Status of amendments

No claim amendments were filed subsequent to final rejection.

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(5) Summary of invention

In one aspect, the invention is hollow vesicles (page 4, lines 14 - 15) having membranes formed from amphiphilic copolymers (polymers having both hydrophobic and hydrophilic segments). The copolymers are triblock copolymers, having an ABA structure, wherein one of A and B is hydrophobic and the other is hydrophilic (page 4, line 28 - page 5, line 15 and pages 6-10).

The vesicles can be made so that they have a hydrophilic inner layer, a hydrophobic middle layer and a hydrophilic outer layer or conversely, a hydrophobic inner layer, a hydrophilic middle layer and a hydrophobic outer layer (page 5, lines 3-8). In another embodiment, the vesicles may be made of copolymers which have a "U-shaped" orientation so that the vesicles have a hydrophobic inner layer and a hydrophilic outer layer, or a hydrophilic inner layer and a hydrophobic outer layer (page 5, lines 8-15).

An active agent may be encapsulated within the vesicle (page 19, line 19 - page 20, line 26) or one or more molecules may be incorporated into the vesicle membrane (page 20, line 27 - page 22, line 5). The vesicle can have a targeting molecule bound to its surface (page 20, line 27 - page 22, line 5). The targeting molecules can be selected from the group consisting of carbohydrates, proteins, folic acid, peptides, peptoids, and antibodies (page 20, line 30 - page 21, line 6).

The vesicles may be biodegradable (page 11, line 26 - page 12, line 16).

In another aspect, the invention is hollow nanocapsules formed by stabilization of the vesicles described above (page 4, lines 16 - 27 and page 18, lines 19 - 24). More specifically, nanocapsules are formed by stabilization of vesicles by end group polymerization of the copolymers (page 4, lines 16-27 and page 18, lines 19-24) or, more generally, via crosslinking of the copolymers (page 4, lines 23-27 and page 18, lines 22-24). The polymerization may be via photopolymerization (page 13, line 32 - page 14, line 21 and page 16, line 1 - page 17, line 26).

The nanocapsules can be made from AB copolymers, wherein one of A and B is hydrophobic and the other is hydrophilic (page 4, line 28 - page 5, line 15 and pages 6-10).

The nanocapsules can have an active agent encapsulated within it (page 19, line 19 - page 20, line 26).

The hollow morphology of the nanocapsules may be preserved when the nanocapsules are dry (page 5, lines 22 - 24 and page 29, lines 6 - 9).

The nanocapsules can be biodegradable (page 11, line 26 - page 12, line 16).

(6) Issues

(i) Whether claim 17 is indefinite under 35 U.S.C. 112, second paragraph, for use of the term "molecule".

(ii) Whether claims 1, 10, 12, 17, and 19 are anticipated under 35 U.S.C. 102(e) by U.S. 6,008,184 ("Pluyter").

(iii) Whether claims 1, 10, 12, 17, and 19 are anticipated under 35 U.S.C. 102(a) by U.S. 5,891,468 ("Martin").

(iv) Whether claims 1, 3-6, 9-14, 16-20, and 27-30 are obvious under 35 U.S.C. 103(a) over WO 97/49387 ("Wooley") by itself or in combination with Martin.

(7) Grouping of claims

The claims stand or fall together.

(8) Argument

(i) Whether claim 17 is indefinite under 35 U.S.C. 112, second paragraph, for use of the term "molecule".

As supported by Exhibit A (Exhibit C in the response filed on July 28, 2003), the common definition of the term molecule is that it is the smallest particle of a compound (a protein, for example) that has the chemical properties of that compound. In fact, "one specific membrane protein" is not made of several molecules as stated by the Examiner. One membrane protein is a single molecule. This use of the term "molecule" is supported in depth in the specification on pages 19-21.

(ii) Whether claims 1, 10, 12, 17, and 19 are anticipated under 35 U.S.C. 102(e) by U.S. 6,008,184 ("Pluyter").

The claims rejected on the basis of Pluyter are drawn to hollow vesicles comprising membranes that are formed from amphiphilic copolymers.

Pluyter teaches using block copolymers in fabric softener compositions to improve the viscosity and stability of the fabric softener. Fabric softeners include lamellar vesicles which are believed to be comprised of alternating concentric layers of water and lamellar cationic bilayers (col. 1, lines 19-21). The block copolymers are added to the lamellar vesicles to stabilize them. The copolymers may be attached to the vesicles or "partially incorporated" within the vesicles (col. 5, lines 32-55) but they do not form the vesicles. In fact, the polymers make up only 0.1 - 10%, most preferably only 0.5 - 2%, of the compositions (col. 3, lines 57-59).

There is no indication in Pluyter that the vesicles are hollow. In fact at col. 1, lines 26-29, the vesicles are described as having an "onion-like configuration of ... concentric bilayers of molecules of fabric softening material with entrapped water or electrolyte solution, the so-called aqueous phase".

It is clear that the claimed invention differs substantially from the cited art in that the membranes of the claimed invention are "formed from amphiphilic copolymers". The compositions taught in Pluyter, comprising lamellar vesicles having, at most 10% block copolymers, can not be said to be "formed from" the copolymers. Moreover, the lamellar vesicles of Pluyter are not hollow- as are the claimed vesicles.

(iii) Whether claims 1, 10, 12, 17, and 19 are anticipated under 35 U.S.C. 102(a) by U.S. 5,891,468 ("Martin").

Martin teaches fusogenic liposomes for delivering agents to the interior of cells. The liposomes are formed from lipids- their membranes are made of lipids. The liposomes have block copolymers attached thereto to enhance fusion with a cell membrane. The block polymer is arranged as a coating of chemically releasable hydrophilic polymer chains and hydrophobic polymers. The hydrophobic chains are initially shielded by the hydrophilic chains and then exposed for fusion with the target cell membrane (see col. 2, lines 45-56). Desirably, the hydrophilic and hydrophobic chains are joined by a chemically releasable bond (see col. 2, lines

57-59). The membranes are not "formed from amphiphilic copolymers", as recited in the present claims. The membranes are formed from lipids. The block polymer is simply on the surface of the liposome.

(iv) Whether claims 1, 3-6, 9-14, 16-20, and 27-30 are obvious under 35 U.S.C. 103(a) over WO 97/49387 ("Wooley") by itself or in combination with Martin.

Wooley Alone

Wooley teaches particles formed from amphiphilic copolymers, having a crosslinked shell and an interior core domain. The hydrophilic portion of the amphiphilic copolymer forms the shell domain and the hydrophobic portion forms the interior core domain, or vice versa (see the abstract and Fig 1, for example).

The globular particles taught by Wooley are micelles wherein the outermost domain is crosslinked (see page 12, lines 5-14 and page 69, lines 4-25). Micelles are commonly formed from amphiphilic molecules, which have a hydrophilic (or hydrophobic) head region and a hydrophobic (or hydrophilic) tail region. The amphiphilic molecules assemble into spherical structures wherein the heads are on the periphery of the micelle and the tails are clustered in the interior. The interior is not empty- the micelles are not hollow.

Methods of making the nanoparticles are described beginning on page 69. One method involves assembling the amphiphilic copolymers into a micellar structure and then crosslinking the outer hydrophilic or hydrophobic heads. These tail regions are clustered in the interior and can also be crosslinked together, in one embodiment.

As further evidence that the nanoparticles taught by Wooley are not hollow, see Exhibits B and C (Exhibits D and E in the response filed July 28, 2003), two articles from the Record, the Washington University in St. Louis school newspaper. Exhibit B, dated May 4, 2000, discusses "knedel" nanoparticles and states that Dr. Wooley had "recently announced" that she had "successfully hollowed out the knedel core to produce 'nanocages' ...". Exhibit C, dated September 14, 2001, states that "In 2000, Wooley and researchers in her lab hollowed out the knedel core to produce 'nanocages'...". These references show that in 1996, when the priority document for Wooley was filed, the microparticles termed "knedels" were not hollow.

Exhibit D (Exhibit F in the response filed July 28, 2003), is provided to show that the "knedels" referenced in the articles of Exhibits B and C are the particles disclosed in Wooley. In the "Materials and Methods" section of the article, the experimental details for the preparation of the SCK (shell crosslinked knedel) structure are provided, citing an article published in 1997 (reference 21), and the description provided in Exhibit D corresponds to the structure described in Example 3 of Wooley.

In support of his argument that the particles of Wooley are hollow, the Examiner points to two sections of Wooley- page 72, lines 19-22 and the paragraph linking pages 85 and 86. On page 72, Wooley states "In preparing particles of the present invention, crosslinking of the shell domain, the interior core domain, or both, can be achieved ...." This statement simply means that the polymer making up the core domain may, or may not be, crosslinked. It does not mean that the "interior core domain" does not exist- i.e. that the core is empty (hollow), it simply means that the core domain can be non-crosslinked material.

The paragraph spanning pages 85 and 86 of Wooley states:

> The pharmaceutically active agent can be present in the particle dissolved in the interior core domain, or covalently attached to a component of the interior core domain, in the form of a fine dispersion within the interior core domain, or on the surface of the interior core domain, or at the interface between the crosslinked shell domain and the interior core domain.

The term "dissolved" does not mean that the interior domain is empty or contains a liquid. See the paragraph directly above the one cited by the Examiner which states that the pharmaceutically active agent can be "dissolved in the crosslinked shell domain". Surely the Examiner will not argue that the crosslinked shell domain is also a liquid. The term dissolved is used in the same way in the paragraphs- to mean that the agent is present in the polymeric domain.

The Examiner's reasoning on page 7 of the Office Action of October 14, 2003 is illustrative of the Examiner's failure to understand the differences between Wooley and the presently claimed invention:

> "Based on this, one can interpret that what is discussed in exhibits D and E is the achievement by the inventors of WO to make the center core totally empty as a cage structure whereas the particles in WO are only partially empty if they are not cross-linked."

This is exactly what is shown by Exhibits D and E (Exhibits B and C in the present document) - the achievement by Wooley et al. of hollow vesicles ("empty as a cage structure") well after the WO was filed. However, the Examiner's statement includes a fallacy- there is no evidence that the particles of Wooley are "only partially empty if they are not cross-linked" as claimed by the Examiner- the evidence to the contrary illustrates that the particles of Wooley are not empty- are not hollow- even when the interior domain is not crosslinked.

The present claims are to "hollow vesicles" and "hollow nanocapsules". Wooley quite simply does not teach or suggest hollow particles.

Wooley in combination with Martin

Martin is discussed above. There really is no reason to combine Martin and Wooley and, even if there were, the claimed invention would not result. What might result if these references were combined is fusogenic micelles- wherein a triblock copolymer is added to the outside of the crosslinked micelles taught by Wooley, in order to increase their fusogenicity (as taught by Martin).

The Examiner states that although Wooley does not teach preparing the particles from triblock polymers, one of ordinary skill in the art would be led to do so because of the teachings of Martin. As discussed above, Martin doesn't teach preparing particles from triblock polymers. Martin teaches preparing fusogenic liposomes. The particles are liposomes made of lipids- to which triblock polymers can be added to increase fusogenicity. Wooley doesn't discuss the need to increase fusogenicity- and Martin doesn't discuss making micelles or particles from amphiphilic copolymers. Even if it did, one would simply be lead to add triblock copolymers to the outside of the micelle or particle- not to form the micelle or particle out of the triblock copolymer.

The incentive to combine references is not present and, even if it were, the claimed invention would not result.

CONCLUSION

None of the references that were cited teach or suggest hollow vesicles or nanocapsules formed from triblock amphiphilic copolymers. None of the references teach or suggest nanocapsules formed by crosslinking these vesicles. Accordingly, it is respectfully submitted that the references are not appropriate as the basis of rejection of the claims.

Respectfully submitted,

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Date: March 15, 2004
404.373.5065

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Collen A. Beard

Date: March 15, 2004

(9) Appendix- Listing of Claims Involved in the Appeal

1. Hollow vesicles comprising membranes formed from amphiphilic copolymers having hydrophobic and hydrophilic segments, wherein the copolymers are ABA copolymers, and wherein one of A and B is hydrophobic and the other is hydrophilic.

3. Hollow nanocapsules formed by stabilization of the vesicles of claim 1.

4. Hollow nanocapsules formed by stabilization of vesicles comprising membranes formed from amphiphilic copolymers having hydrophobic and hydrophilic segments, wherein the vesicles are stabilized by end group polymerization of the copolymers.

5. The nanocapsules of claim 3, wherein the vesicles are stabilized via crosslinking of the copolymers.

6. The nanocapsules of claim 4, wherein the copolymers are AB copolymers, wherein one of A and B is hydrophobic and the other is hydrophilic.

9. The nanocapsules of claim 4, wherein an active agent is encapsulated within the nanocapsule.

10. The vesicles of claim 1, wherein an active agent is encapsulated within the vesicle.

11. The nanocapsules of claim 3, wherein an active agent is encapsulated within the nanocapsule.

12. The vesicles of claim 1, wherein the vesicles comprise a hydrophilic inner layer, a hydrophobic middle layer and a hydrophilic outer layer.

13. The vesicles of claim 1, wherein the vesicles comprise a hydrophobic inner layer, a hydrophilic middle layer and a hydrophobic outer layer.

14. The vesicles of claim 1, wherein the copolymers are U-shaped and the vesicles have a hydrophobic inner layer and a hydrophilic outer layer, or a hydrophilic inner layer and a hydrophobic outer layer.

16. The nanocapsules of claim 4, wherein the polymerization is via photopolymerization.

17. The vesicles of claim 1, wherein one or more molecules are incorporated into the vesicle membrane.

18. The nanocapsules of claim 3, wherein the hollow morphology of the nanocapsules is preserved when the nanocapsules are dry.

19. The vesicles of claim 1, wherein the vesicles are biodegradable.

20. The nanocapsules of claim 3, wherein the nanocapsules are biodegradable.

27. The vesicles of claim 1 further comprising targeting molecules bound to the surface of the vesicles.

28. The vesicles of claim 27 wherein the targeting molecules are selected from the group consisting of carbohydrates, proteins, folic acid, peptides, peptoids, and antibodies.

29. The nanocapsules of claim 4, wherein the hollow morphology of the nanocapsules is preserved when the nanocapsules are dry.

30. The nanocapsules of claim 4, wherein the nanocapsules are biodegradable.